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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/520,791 | 01/08/2005 | Alexander Domling | 62660(52171) | 3248 |

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| EXAMINER | |
|---|---|
| GUDIBANDE, SATYANARAYAN R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,791 | DOMLING ET AL. | |
| | Examiner | Art Unit | |
| | Satyanarayana R. Gudibande | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7-20* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10,12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendments to claims filed on 4/24/06 and the addition of new claims 18-20 is acknowledged.

Any objections and or rejections not specifically addressed are herein withdrawn.

Claims 7-20 are pending in the application.

Claim 11 remains withdrawn from consideration as being drawn to non-elected species.

This application contains claim 11 drawn to a species nonelected with traverse in Paper No. dated 01/23/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 7-10, 12-20 have been examined on the merits.

### *Response to Arguments/Remarks*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-10, 14, 15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sasse, et al., The Journal of Antibiotics, 2000, 53, 879-885, in view of Greenwald, Journal of Controlled Release, 2001, 74, 159-171 as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicants argue that the primary citation does not teach linker pegylation of the molecule. Applicants argue that Examiner assumed that a linker or spacer arm is introduced into the compound of the general formula U-V-W by using the activated PEG molecule. Applicants have indicated that the Greenwald reference teaches conjugates of drugs with higher molecular weight PEG (>20,000d).

Applicant's arguments filed 4/24/06 have been fully considered but they are not persuasive. Applicant's argument that the primary citation does not teach linker pegylation of the molecule is moot. It should be pointed out here that Examiner is making an obviousness type rejection. If the primary reference of Sasse, et al., had taught pegylation of tubulysin molecule it would have been an anticipation rejection.

Applicant's argument that Examiner assumed that a linker or spacer arm is introduced into the compound of the general formula U-V-W by using the activated PEG molecule is not persuasive. In accordance with election of species requirement, applicant was required to elect a single species indicating all the variables that would define a single species. To satisfy this requirement, instead of electing a species as required by the election of species, applicants elected molecular formula represented in claims 14 and 17. As per applicant's election of

species, if 'V' is the linker according to applicant, it should come from the tubulysin molecule. Primary reference of Sasse, et al., discloses such a molecule wherein 'V' could be the oxygen 'O' of the carboxylic acid functional group. In addition to this, applicant uses the method described in the publication **Greenwald, Bioorg. Med. Chem., 1998, 6, 551-562,** for the preparation of pegylated molecule of tubulysin. The cited publication of record by the Examiner, **Greenwald, Journal of Controlled Release, 2001, 74, 159-171** teaches similar linkers and activation chemistries for the pegylation of the drug molecules. Therefore, the use of activated PEG molecules introduces linker or spacer arm.

Applicants have indicated that the Greenwald reference teaches conjugates of drugs with higher molecular weight PEG (>20,000d). This argument is moot in light of the aforementioned response to arguments. Because, the applicant uses the synthetic methods described in the Greenwald reference to synthesize their tubulysin conjugates.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 16-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicant's arguments filed 4/24/06 have been fully considered but they are not persuasive. Because, as pointed earlier, applicants claim numerous modified tubulysin

compounds. Applicants have shown the synthesis of three variants of pegylated tubulysin molecules with tubulysin A as the starting compound. Applicants have not disclosed any synthetic procedures to synthesize number of modified, or derivatives of the tubulysin compounds. As indicated in our previous office action, applicants have not provided guidance as to how the numerous variants of tubulysins are synthesized or isolated from different strains of microorganisms.

There is no structure-function correlation to show which of these numerous variants will have desired anticancer activity. The Board of Appeals has held *Ex parte Sudilovsky,* that a disclosure was non-enabling since:

"[t]he specification, though highly detailed , is devoted solely to a description of compounds stated to be known ACE inhibitors. The remainder of the specification is directed to how to make tablets and solutions for injection. Any disclosure regarding utility is confined to broad allegations and suggestions without substantiating working example. As stated in *In re Glass,* 49 F.2d 1228, 181 USPQ 31, 35 (CCA1974), 'the strong feeling one gets from reading the entire specification is that either appellant did not have possession of the details of a single operative process or, if he did, he chose not to divulge them."

*Ex parte Sudilovsky,*21 USPQ2d 1702 (BPAI 1991). Similarly, the the disclosure of the instant application with regard to the biological activity is confined to broad allegations and suggestions without substantiating working examples. Although working examples are not necessary in the specification, lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable art. When an applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk

that unless one of ordinary skill in the art would accept the allegations as obviously valid and correct. In the instant application, specification has not provided evidence of record of a single compound that would exhibit anticancer activity. Therefore, one skilled in the art would not be able to practice the invention as disclosed by the applicants.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654